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Validation of asthma and eczema in population-based Swedish drug- and patient registers

Running head

Validation of asthma and eczema in Swedish registers

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Keywords

allergic diseases, asthma outcomes research, asthma pharmacology, disease proxy, nationwide, prescription prevalence

Key points

- The population-based Swedish Prescribed Drug Register (SPDR) and National Patient Register (NPR) are excellent sources of information for epidemiological association studies.
- Asthma medication reported in the SPDR is a suitable proxy for asthma both in children and adults, but the same approach is insufficient for eczema.
- The quality of asthma diagnoses in the NPR can be considered high, since approximately all school-age children fulfilled predefined criteria of asthma.

Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

ATC – Anatomical Therapeutic Chemical (ATC) classification system

ICD-10 – International Classification of Disease, version 10

NBHW – National Board of Health and Welfare

NPR – Swedish National Patient Register

PIN – Personal Identification Number

PPV – positive predictive value

PHCC - Primary Health Care Centres

SPDR – Swedish Prescribed Drug Register

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Abstract

Purpose

Validated measures of asthma and eczema at the population level remain a challenge. Our aim was to ascertain if register-based information on asthma/eczema medication can function as a proxy for an asthma/eczema diagnosis and to validate register-based asthma diagnoses.

Methods

Information was requested on all 0-45 year old individuals with reported asthma/eczema medication and/or diagnoses in the Swedish Prescribed Drug Register and National Patient Register, between July 2005 and December 2009 (N=250,691). Medical records for 1,952 individuals were reviewed to estimate the proportion of individuals with 1) asthma/eczema medication that fulfilled predefined criteria of asthma/eczema (positive predictive value (PPV); 2) a register-based asthma diagnosis verified as asthma by set criteria.

Results

PPV for asthma by predefined criteria ranged between 0.75 (95% CI: 0.70-0.78) to 0.94 (95% CI: 0.91- 0.96) depending on age-group. PPV for eczema was estimated to 0.45 (95% CI: 0.38-0.51). Eighty percent of children 0-4.5 years and 99% of children >4.5-17 years with a register-based diagnosis of asthma were verified as asthmatics.

Conclusion

Asthma medication is a suitable proxy for asthma in older children and adults; the same approach is insufficient for eczema. This validation study of two Swedish registers opens for future large nation-wide register-based studies on asthma.

Introduction

Asthma and eczema are two of the most common chronic childhood diseases in the world ^{1, 2}.

Asthma is an inflammatory disease of the airways with a prevalence of about 8-10% in children and 6-8% in adults in Sweden ^{3, 4}. Eczema, manifesting as chronic itchy flexural rashes affects about 20% of all Swedish children ².

Valid measures of asthma and eczema at the population level remain a challenge ⁵. Most epidemiological studies investigating asthma and eczema have previously used questionnaires to identify these diseases ⁶. Questionnaires are often restricted to specific areas or age-groups and can be susceptible to culture- and language-related issues associated with translation and interpretation ^{7, 8}. Due to ethical, economical and practical reasons a standardized clinical examination of individuals with and without asthma/eczema is not feasible in large-scale studies. Thus, validated population-based register data can function as a proxy, when aiming to study the diseases in the total population.

The Swedish National Board of Health and Welfare (NBHW) holds several population-based health registers, such as the Swedish Prescribed Drug Register (SPDR) ⁹ and the National Patient Register (NPR) ¹⁰, covering the entire Swedish population (9 million inhabitants). Since July 2005, all dispensed prescriptions are reported to the SPDR. All diagnoses from the in-patient care and 75% of specialized out-patient care are reported to the NPR since 1964 and 2001 respectively, whereas diagnoses from primary health care centres (PHCC) are not recorded on a national level. To identify individuals with asthma and eczema in Sweden that have visited a physician at a PHCC, these diagnoses could be conveniently identified in the SPDR which allows identification of specific drugs for treatment of specific diseases.

Previous studies have validated asthma medication as a proxy for asthmatic disease in children ¹¹⁻¹⁴ and adults ¹⁴⁻¹⁶ by reviewing medical records from general practitioners (GPs) ^{12, 15, 16} or through retrospective questionnaires to GPs ¹¹ and paediatricians ¹³ in limited regions. Others have suggested that prescription prevalence of asthma medication could function as a measure of disease prevalence in children ¹⁷ and adults ¹⁸. Until now, there is no population-based study that has used randomly selected medical records on a national level to validate an asthma diagnosis with pre-defined criteria based on dispensed prescriptions of asthma medications. Some Swedish studies have already used asthma medication as a proxy for asthmatic disease ¹⁹⁻²², but so far no one has validated the Swedish data. Additionally, the authors have not been able to identify any study that has investigated the opportunity of using prescription data on eczema medication as a proxy for eczema.

To enhance the strength and quality of register-based research and in order to obtain generalizable findings in large populations, validation of register data is needed. Therefore, the aim of this study was to 1) describe the utilization of asthma/eczema medication in Sweden; 2) validate if medication for asthma/ eczema can function as a proxy for an asthma/eczema diagnosis respectively, by reviewing medical records corresponding to dispensed medications in the SPDR, according to doctor-diagnoses and predefined criteria by the Swedish Paediatric Society's section for Allergy ²³; and 3) validate asthma diagnoses in children in the NPR, by investigating how a reported diagnosis of asthma corresponds to set criteria ²³.

Method

Study design and population

This was a nationwide population-based register study using information from the SPDR, the NPR and medical records from PHCC and hospitals all around Sweden.

The SPDR is one of the largest population-based drug registers in the world⁹. It provides complete data on dispensed drugs regardless of age, gender, prescribing physician and reimbursement status. All pharmaceuticals are classified according to the Anatomical Therapeutic Chemical classifications system (ATC). The NPR includes information on primary and secondary diagnoses, according to the International Classification of Disease (ICD) system. The universal use of the personal identity number (PIN)²⁴ enables a linkage between the SPDR and NPR.

Encrypted information on all individuals, 0-45 years of age, that had filled at least one prescription of asthma and/or eczema medication (**aim 1**) and/or had been given a diagnosis of asthma (ICD 10 code J45) and/or eczema (ICD 10 code L20) between July 2005 and December 2009, was requested from the NBHW. Information on the patients' age, sex, prescription- and dispensing date, data on dispensed item and amount (SPDR) and discharge date (NPR), was also requested. Medications of interest were inhalations of selective β 2-adrenoreceptor agonists (ATC: R03AC), glucocorticoids (R03BA) and fixed combinations of β 2-agonists and glucocorticoids (R03AK), leukotriene receptor antagonists (R03DC), glucocorticoids for external use (D07A) and the immunosuppressant tacrolimus (D11AH01) and pimecrolimus (D11AH02). Oral β 2-agonists (R03C) were not included.

Figure 1 displays the linkage between the SPDR and the NPR and the inclusion criteria for the study population. To validate asthma/eczema medication in the SPDR as a proxy for an asthma/eczema diagnosis, all individuals with filled prescriptions of asthma/eczema medication without a diagnosis of asthma/eczema in the NPR, were identified

and grouped based on the age at the date of a given prescription (asthma-medication: 0-4.5; >4.5-17; 18-45 years; eczema-medication: 0-17 years), as well as number of filled prescriptions and type of prescribed medication. The reason for excluding individuals with a diagnosis of asthma/eczema was to ascertain the possibility of using SPDR as a complementary source of information to the NPR. To avoid one-time asthma medication users, at least two or more prescriptions were needed, as well as with a time frame of two weeks between prescriptions for the pre-school children. To validate the diagnosis of asthma in the NPR two groups of children (0-4.5; >4.5-17 years) with a diagnosis of asthma, independent of history of asthma medication, were furthermore identified.

Collection and assessment of medical records

Random samples from all groups were sent to NBHW and PINs requested. The study participants' medical records corresponding to the dates of prescriptions of the asthma/eczema medication (**aim 2**), or corresponding to the discharge date from the hospital (**aim 3**), were requested by a letter to the head of the unit/ward where the patient had been treated. Two reminder letters were sent out before the end of data collection.

The diagnosis that each patient had been assigned by the physician at each consultation connected to the date of the prescribed medication was extracted from the medical records. Diagnoses of special interest for the asthma part were asthma (J45), acute bronchitis/bronchiolitis (J20/J21) and chronic bronchitis/chronic obstructive pulmonary disease (COPD) (J42/J44).

Furthermore, medical records belonging to pre-schoolers (0 – 4.5 years) and school-age children (>4.5 – 17) in the asthma medication validation and asthma diagnosis validation, were combined and reviewed by authors AÖ and CA according to the criteria of asthma set by the Swedish Paediatric Society²³, where asthma is defined as ≥ 3 obstructive periods before two years of age and/or; ≥ 1 obstructive period after two years of age and/or; \geq

1 obstructive period independent of age when the child has ≥ 1 of the following: eczema, allergy or no improvement between periods of respiratory tract infections. Children under two years of age with ≤ 2 asthma-like symptoms during respiratory tract infections, without symptoms between infections, were defined as suffering from obstructive bronchitis. Individuals without recorded patient history (eg. only a renewal of a prescription) in any medical record were excluded in the analysis of PPV based on the criteria by the Swedish Paediatric Society.

Records in the eczema part were firstly reviewed to assess whether the child had the “umbrella diagnosis” dermatitis, which was defined as either having been assigned the diagnosis unspecific dermatitis (L30.9) by a physician or if having been given either sub-diagnosis of dermatitis such as eczema (L20), allergic/non-allergic contact dermatitis (L23-L25) or seborrhoeic dermatitis (L21) assigned by the physician. Secondly, each assigned sub-diagnosis of dermatitis was analysed separately.

Statistical analysis

To describe the utilization of asthma/eczema medication in Sweden, period prevalence of drug users was estimated as the proportion of individuals in the Swedish population for whom medication was dispensed during year 2008. The number of individuals were retrieved from Statistics Sweden ²⁵.

Incidence estimates were based on all new users of anti-asthmatic drugs between 2008-2009 and estimated person-time based on population data from Statistics Sweden ²⁵ with 95% confidence intervals calculated assuming poisson distribution. The time period was based on the waiting-time distribution ²⁶, which is a frequency distribution of first time occurrences of drug use within a time-window. *Figure 2* shows the monthly frequencies of first appearances of filled prescriptions for all persons who have redeemed anti-asthmatic

prescriptions July 2005-December 2009, according to the appearance of their first filled prescription within the period. In the beginning of the period there is a mixture of old and new users. The frequencies thereafter decrease until it levels out. At this point it's mostly new (incident) users that appear. The time period used for incidence estimation has to be beyond this point in time to avoid prevalent users to be included in the calculations.

To validate reported asthma/eczema medication in the SPDR as a proxy for an asthma/eczema diagnosis, positive predictive value (PPV) was estimated as the proportion of children and adults that had been given a diagnosis of asthma/eczema (as well other asthma-like and dermatitis-like diagnoses) in each medication validation group with asthma/eczema medication. PPV was also estimated as the proportion of pre-schoolers and school-age children with asthma medication that fulfilled the criteria of asthma set by the Swedish Paediatric Society. The sample size in each group was determined based on an expected PPV of 75% and aim of 95% confidence intervals of $\pm 5\%$ -units.

To validate the diagnosis of asthma in children in the NPR, the proportion of children that had been given a diagnosis by a physician that fulfilled the criteria of asthma, was calculated.

Statistical Analysis Software 9.3 (SAS Institute, Cary, NC) was used for all analyses. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Results

Prevalence and incidence

Table 1 shows the period prevalence of anti-asthmatic drugs in year 2008 in Sweden. In total, 282,826 individuals between 0-45 years of age redeemed approximately 890,000 prescriptions of anti-asthmatic drugs. The period prevalence decreased from 7.8% in pre-school children to 5.9% in school-age children and 4.7 % in adults. Males were more commonly prescribed asthma medication in childhood, whereas females dominated in adulthood. The most commonly prescribed anti-asthmatic drug in all age groups was inhalations of selective β_2 -adrenoreceptor agonists. *Table 1* also displays the numbers for drugs used to treat eczema. The period prevalence of drugs against eczema also decreased with increasing age. Mild glucocorticoids (GC) was the most commonly filled drug against eczema in children 0-4.5 years, moderate GC in children >4.5-17 years and potent GC in adults.

Figure 2 presents the number of “new” unique subjects having redeemed anti-asthmatic drugs for each month July 2005-December 2009. The incidence of new anti-asthmatic drug users was assessed after a wash-out period of 30 months. The estimated number of person-years 2008-2009 in pre-school children was 980,011; in school-age children 2,865,921; and in adults 6,874,703. In total, 36,779 pre-school children were defined as new users during 2008-2009 thus rendering an incidence of 3.75/100 person-years (95% Confidence Interval (CI): 3.71- 3.79). For school-age children the number of new users was 55,261 corresponding to an incidence of 1.93/100 person-years (95% CI: 1.91-1.94) and in adults 102,487 users were found to give an incidence of 1.49/100 person-years (95% CI: 1.48-1.50).

Asthma medication as a proxy for asthma diagnosis

Table 2 displays number of identified individuals in each study group, number of individuals for whom medical records were requested and retrieved. In total 250,691 individuals fulfilled

the inclusion criteria and requests for 2,600 patients' medical records were sent out. In total, 998 units/wards for the asthma medication validation; 330 for the eczema medication validation; and 119 for the asthma diagnosis validation, were contacted. We obtained data on 1,952 patients (75%).

Table 2 also shows the response rates of received medical records, where the highest response rates were found in pre-schoolers (0-4.5 years: 87%) and school-age children (>4.5-17 years: 83%) in the validation of asthma diagnoses in the NPR. The lowest response rate of 66% corresponds to school-age children in the asthma medication validation. Reasons for no response were; 1) head of unit did not want to participate in study; 2) health care centre has ceased to exist; 3) no medical charts could be found at the unit; 4) requests were sent in return.

Table 3 displays the PPV in the asthma medication validation, for a doctor-diagnosis of asthma and other “asthma-like” diseases such as acute/chronic bronchitis in received medicals records. PPV for a doctor-diagnosed asthma was 89% in both school-age children (4.5-17 years) and adults (18-45), whereas PPV for pre-schoolers was 68%. The PPV for doctor-diagnosed acute bronchitis/bronchiolitis in pre-schoolers was 26%, while a PPV of less than one percent was seen for COPD/chronic bronchitis independent of age group. The groups based on type of diagnosis, are not mutually exclusive since more than one record per patient was requested, and each record was reviewed to identify the diagnosis given at each consultation.

Among pre-school children without an asthma diagnosis recorded in any medical record (n=166), approximately 38% had been given a diagnosis of acute bronchitis/bronchiolitis by their physicians. Corresponding number in school-age children was 14% (9 of 66). Three adults had been given a COPD diagnosis at one consultation, but all three had also been given a diagnosis of asthma at other occasions (not tabulated).

Table 3 also shows PPV based on the asthma criteria by the Swedish Paediatric Society, assessed by combined information from all retrieved medical records for each individual. The pre-schoolers had a PPV of 75% for asthma, while school-age children (>4.5-17 years) had a PPV of 94%. When combining pre-schoolers defined as asthmatics with children defined as having obstructive bronchitis, PPV increased to 87%. Approximately 6% (31 of 486) of pre-school children and 9% (34 of 395) of school-age children had missing information on the indication of the prescription and were therefore excluded in the analysis of PPV based on asthma criteria for children. Corresponding number for missing information in adults was 19% (44 of 234).

Of the pre-school children that did not fulfil the asthma criteria, 18% (84 of 455; after exclusion of individuals with missing information) were defined as having obstructive bronchitis by criteria, and 7% (32 of 455) as having been given asthma medication for other reasons such as cough or upper respiratory tract infections. All school-age children that did not fulfil the asthma criteria (6%) had been given a prescription for other reasons (not tabulated).

Eczema medication as a proxy for eczema diagnosis

Table 4 shows PPV for the “umbrella diagnosis” dermatitis and the sub-diagnoses eczema, seborrhoeic dermatitis and contact dermatitis found in medical records based on medication in the SPDR. A PPV of 82% was estimated for dermatitis, while PPV was estimated to be 45% for the specific diagnosis of eczema (L20). Approximately 7% (17 of 242) of the children included in the eczema medication validation were lacking information on the indication for the prescription.

Validation of asthma diagnoses in the NPR

In the validation of asthma diagnoses in children in the NPR, about 78% of the pre-schoolers (0-4.5 years) fulfilled the asthma criteria set by the Swedish Paediatric Society. The ones that did not fulfil the asthma criteria were almost all defined as suffering from obstructive bronchitis (21%). In school-age children (>4.5-17 years) almost everyone (99%) fulfilled the asthma criteria (not tabulated).

Discussion

Our results show relatively high positive predictive values for asthma in all age groups which suggest that asthma medication reported in the SPDR can function as a suitable proxy for a doctor-diagnosed asthma, as well as for asthma by criteria according to the Swedish Paediatric Society. Our results bring new possibilities to study asthma in all children and young adults in Sweden and support previous findings in association studies which have used asthma medication as an indicator for asthma ¹⁹⁻²². Furthermore, the quality of doctor-diagnosed asthma in the NPR can be considered to be high, since almost eighty percent of pre-school children and all school-age children with asthma reported in the NPR fulfilled the asthma criteria set by the Swedish Paediatric Society.

Previous studies on asthma medication as a proxy for asthmatic disease ^{11-16, 18, 27} have been restricted to small sample sizes ¹⁴, specific regions ^{11, 13, 16} or used prescribed medications instead of filled prescriptions of medication ^{12, 15}. The novelty with this study is the population-based design, where randomly selected medical records on a national level have been reviewed both to assess doctor-diagnosed asthma and asthma by criteria. Concerns against asthma medication as a proxy for asthma have been that asthma medication is often prescribed to wheezing infants and the response to the drugs is used as a diagnostic tool for asthmatic symptoms ²⁸. Therefore, we only included individuals with at least two records of prescribed asthma medication.

In this first study to evaluate eczema medications as a proxy for a diagnosis of eczema, PPV for the “umbrella diagnosis” of dermatitis was rather high. On the other hand, the PPV estimated for an eczema diagnosis specifically was quite low. This indicates that using eczema medication as proxy for eczema may induce misclassification bias and the proxy should be used with caution. The World Allergy Organization recommends that under

the “umbrella term” dermatitis, eczema should replace the intermediate term atopic eczema/dermatitis syndrome. Further classification into atopic eczema should only be made after determination of Immunoglobulin E, antibodies or skin prick testing ²⁹. Review based on validated standardized definitions for eczema ³⁰ was impossible due to lacking information and we could only calculate PPV for all diagnoses under the umbrella term dermatitis and each sub-diagnosis separately.

This is the first study to show population-based data on the utilization of anti-asthmatic drugs in Swedish children and so far, there are no studies to our knowledge that have shown population-based data on utilization of drugs to treat eczema. Questionnaire-based studies with parental reports of atopic eczema have a prevalence of approximately 20% ². This is a much higher number than the prescription prevalence for any investigated eczema medication in the present study. In Sweden, over-the-counter (OTC) drugs for treatment of eczema can be purchased and it is possible that children with mild symptoms might have either not been treated at all or have only used OTC drugs and are therefore not included in our data.

The main strengths of this study include our nationwide population-based study design and the randomly selected patients to be included in the review of their medical records. By using random sampling, we were able to avoid selection bias in terms of regional differences and socio-economic status affecting prescribing habits ²⁶. The SPDR is population-based and provides complete data. Even though our study period is limited to the start of the SPDR in 2005, we were able to avoid influences of seasonal variance. Furthermore, the medical records in the medication validation of asthma were both reviewed in terms of doctor-diagnosis of asthma and based on criteria.

We were not able to estimate PPV for different types of asthma, which is one limitation in this study. Furthermore, our results with a lower PPV for asthma in pre-

schoolers, could represent the widely recognized picture of young wheezers³¹. A diagnosis of asthma becomes more accurate with increasing age²⁸ and while our criteria for asthma is one of this study's strengths, it can also be questioned since it includes both children with infection-induced symptoms some of which have signs of allergy, and a group of children with allergic asthma with varying prognosis³². However, the obstructive symptoms for infection-induced and allergic asthma are fairly similar. Furthermore, children with infection-induced asthma belong to the majority of children with asthma in hospital care³³, and are important to include in a proxy for the disease to identify as many true asthmatics as possible, independent on their prognosis.

There was a slight difference in PPV between a doctor-diagnosis of asthma and asthma according to our criteria in the validation of asthma medication, which could be explained by the fact that we were able to combine information from several medical records, giving us the possibility to study the patient over time. Our values of PPV would probably have increased if we had access to medical records from other occasions than just for the consultation where a prescription was given, due to that asthma is a chronic disease and physicians might not give the patient a diagnosis at each consultation; neither prescribe medication at each visit where a diagnosis is given. The snap-shot study design can also explain why not all children with an asthma diagnosis in the NPR could be verified as asthmatics.

In the adult population, less than two percent had been given a diagnosis of COPD by their physicians, which corresponds to previous reported prevalence of COPD in young adults in the European Community Respiratory Health Survey³⁴. We cannot dismiss the fact that the adults, where an indication for a prescription was missing, did not suffer from COPD. However, by excluding adults above 45 years of age, the risk that COPD has biased our results, is diminished.

In conclusion, our study suggests that asthma medication in the SPDR can be used as proxy for asthma, but not for eczema. This validation study of two Swedish registers opens for future large nation-wide register-based studies on asthma.

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Tables

Table 1. Period prevalence (year 2008) of anti-asthmatic/eczema medication* in children and adults 0-45 years of age. Number of individuals in each age group in the Swedish population was retrieved from Statistics Sweden [‡].

	Age group					
	0-4.5		>4.5-17		18-45	
Asthma (R03)*						
Total number of individuals	37 826		84 598		160 402	
Sex (n, %)						
Male	23 362 (61.8)		48 383 (57.2)		68 426 (42.7)	
Female	14 464 (38.2)		36 215 (42.8)		91 976 (57.3)	
Total number of filled prescriptions for drugs for obstructive airway disease	134 021		253 758		499 704	
Prevalence (%) Male; Female						
<i>Drugs for obstructive airway diseases</i>	9.4	6.1	6.5	5.2	3.9	5.5
<i>Inhalations of selective β2-adrenoreceptor agonists</i>	4.8	3.1	3.3	2.9	2.1	3.0
<i>Adrenergics and other drugs for obstructive airway diseases, combinatios</i>	0.1	0.04	1.0	0.7	0.8	1.0
<i>Inhalation of corticosteroids</i>	4.0	2.7	1.9	1.4	0.9	1.3
<i>Leukotriene receptor antagonists</i>	0.3	0.2	0.3	0.2	0.1	0.1
Eczema (D07A, D11AH01, D11AH02)*						
Total number of individuals	32 757		55 307		141 728	
Sex (n, %)						
Male	18 116 (55.3)		27 277 (49.3)		59 241 (41.8)	
Female	14 641 (44.7)		28 030 (50.7)		82 487 (58.2)	
Total number of filled prescriptions of glucocorticoids for external use	54 238		8900		243 740	
Total number of filled prescriptions of topical immunosuppressants	577		2536		6038	
Prevalence (%) Male; Female						
<i>Glucorticoids for external use</i>	7.2	6.2	3.6	3.9	3.3	4.9
<i>Glucorticoids for external use, mild (1)</i>	3.8	3.2	0.9	1.0	0.3	0.5
<i>Glucorticoids for external use, moderate (2)</i>	2.4	2.2	1.2	1.5	0.8	1.2
<i>Glucorticoids for external use, potent (3)</i>	0.8	0.7	1.2	1.4	2.0	2.7
<i>Glucorticoids for external use, very potent (4)</i>	0.2	0.02	0.4	0.1	0.3	0.4
<i>Tacrolimus</i>	0.1	0.1	0.1	0.1	0.1	0.1
<i>Picremolimus</i>	0.02	0.02	0.01	0.02	0.01	0.02

¥ Swedish population in 2008:

0-4.5 years: 249,052 (males); 235,537 (females)

4.5-17 years: 739,293 (males); 700,958 (females)

18-45 years: 1,744,498 (males); 1,671,429 (females)

* Description of ATC codes for pharmaceuticals

R03 – drugs for obstructive airway diseases

R03AC – selective β 2-adrenoreceptor agonists

R03AK – fixed combinations of β 2-agonists and corticosteroids

R03BA – inhalations of corticosteroids

R03DC – Leukotriene receptor antagonists

D07 – glucocorticoids for external use

D07AA – glucocorticoids for external use, group 1

D07AB – glucocorticoids for external use, group 2

D07AC – glucocorticoids for external use, group 3

D07AD – glucocorticoids for external use, group 4

D11AH01 – immunosuppressant Tacrolimus

D11AH02 – immunosuppressant Picremolimus

Table 2. Study base that fulfilled inclusion criteria (N) in each group and number of patients for whom medical records were requested and retrieved.

	Anti-asthmatic drugs SPDR			Eczema drugs SPDR	Asthma diagnosis NPR	
Age years (group)	0-4.5 (1)	>4.5 – 17 (2)	18-45 (3)	0-17 (4)	0-4.5 (5)	>4.5 -17 (6)
Study base, N	10 001	16 853	128 747	40 364	28 248	26 478
Number of patients for whom medical records were requested, n	600	600	350	350	350	350
Number of patients for whom medical records were retrieved, n (%)	486 (81.0)	395 (65.8)	234 (66.9)	242 (69.1)	306 (87.4)	289 (82.6)
Sex, n (%)						
<i>Male</i>	281 (57.8)	203 (51.4)	93 (39.7)	115 (47.5)	202 (66.0)	155 (53.6)
<i>Female</i>	205 (42.2)	192 (48.6)	141 (60.3)	127 (52.5)	104 (34.0)	134 (46.4)

Table 3. Positive Predictive Value (PPV) and 95% Confidence Interval (CI) estimated as the proportion of individuals with asthma medication with a doctor-diagnosed asthma or asthma-like diagnoses. PPV and 95% CI estimated as the proportion of pre-schoolers and school-age children with asthma medication that fulfilled the criteria of asthma or asthma in combination with obstructive bronchitis according to criteria by the Swedish Paediatric Society.

Age (years)						
	0-4.5		>4.5-17		18-45	
Doctor-diagnosis						
<i>n; PPV (95% CI)</i>						
Asthma (J45)	320	0.68 (0.64-0.72)	329	0.89 (0.85-0.92)	171	0.89 (0.83-0.93)
Acute Bronchitis and bronchiolitis (J20/J21)	123	0.26 (0.22-0.30)	16	0.04 (0.02-0.07)	11	0.06 (0.03-0.10)
Chronic bronchitis and COPD (J42/J44)	1	0.002 (0.0001-0.01)	0	-	3	0.02 (0.003-0.04)
Diagnosis by criteria^{*‡}						
<i>n; PPV (95% CI)</i>						
Asthma	339	0.75 (0.70- 0.78)	340	0.94 (0.91- 0.96)	-	-
Asthma or obstructive bronchitis	415	0.87 (0.83- 0.90)	-	-	-	-

* ≥ 3 obstructive periods before 2 years and/or ≥ 1 obstructive period after 2 years and/or ≥ 1 obstructive period independent of age, where the child has eczema, food allergy, other allergies, or if the child does not get better between periods of respiratory tract infections. Children under two years of age with asthma-like symptoms during respiratory tract infections, but without symptoms between infections, were defined as suffering from obstructive bronchitis.

[‡] Individuals where no information was available at all, were excluded in the analysis of PPV based on criteria.

Table 4. Positive Predictive Value (PPV) and 95% Confidence Interval (CI) estimated as the proportion of children 0-17 years of age with filled prescriptions of pharmaceuticals of topical glucocorticoids or immunosuppressants that were assessed as having a diagnosis of unspecific dermatitis and sub-diagnoses of dermatitis.

Diagnosis	Age (years)	
	0-17	
	n	PPV (95% CI)
Dermatitis*	199	0.82 (0.77-0.87)
Eczema (L20)	108	0.45 (0.38-0.51)
Seborrhoeic dermatitis (L21)	17	0.07 (0.04-0.11)
Contact dermatitis (L25); allergic (L23) and non- allergic (L24)	7	0.03 (0.02-0.06)

*Includes all children who were reviewed as either having been given a diagnosis of unspecific dermatitis (L30.9) by their physician specifically or if having been assigned any of the other diagnosis under the “umbrella diagnosis” of dermatitis, such as eczema, seborrhoeic dermatitis and contact dermatitis. Since all children with a sub-diagnosis of dermatitis are included in the group dermatitis, PPV for all groups together exceeds 100%.

Figures

Figure 1. Through a linkage between the Swedish Prescribed Drug Register and National Patient Register, six groups of individuals were identified based on age at prescription, type and number of filled prescriptions of asthma/eczema medication without a diagnosis of asthma/eczema (aim 2: group 1-4), or based on a diagnosis of asthma independent on history of medication (aim 3: group 5 and 6). The figure displays inclusion criteria for each group (1-6).

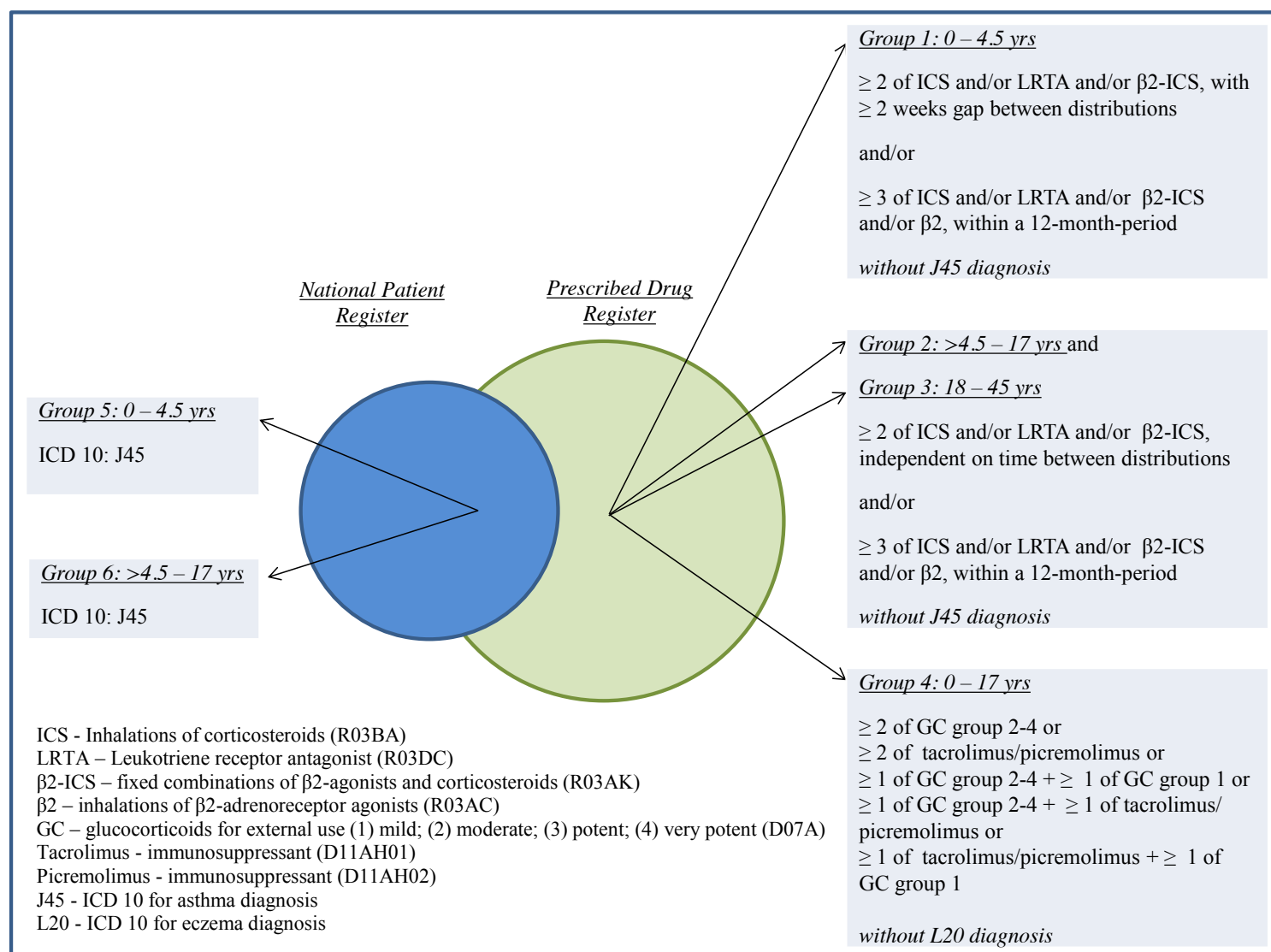


Figure 2. Number of individuals with first time filled prescriptions of ATC group R03 (excluding R03C), for children and adults each month, between July 2005 and December 2009. The years of 2008-2009 were considered in the analysis of incidence.

